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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DISEASE RELATED PROTEIN NETWORK

(57) Abstract: The present invention relates to a method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide comprising the steps of (a) contacting a selection of (poly)peptides suspected to contain one or several of said direct or indirect interaction partners with said disease-related (poly)peptides and optionally with known direct or indirect interaction partners of said diseaserelated (poly)peptide under conditions that allow the interaction between interaction partners to occur; (b) detecting (poly)peptides that interact with said disease-related (poly)peptide or with said known direct or indirect interaction partners of said disease-related (poly) peptide; (c) contacting (poly)peptides detected in step (b) with a selection of (poly) peptides suspected to contain one or several (poly)peptides interacting with said (poly)peptides detected in step (b) under conditions that allow the interaction between interaction partners to occur; (d) detecting proteins that interact with said (poly) peptides detected in step (b); (e) contacting said disease related (poly)peptide and optionally said known direct or indirect interaction partners of said disease-related (poly)peptide, said (poly)peptides detected in steps (b) and (d) and a selection of proteins suspected to contain one or several (poly)peptides interacting with any of the afore mentioned (poly)peptides under conditions that allow the interaction between interaction partners to occur; (f) detecting (poly)peptides that interact with said disease-related (poly)peptide and optionally said known direct or indirect interaction partners of said disease-related (poly)peptide or with said (poly)peptides identified in step (b) or (d); and (g) generating a (poly)peptide(poly)peptide interaction network of said disease-related (poly)peptide and optionally said known direct or indirect interaction partners of said disease-related (poly)peptide and said (poly)peptides identified in steps (b), (d) and (f). Moreover, the present invention relates to a protein complex comprising at least two proteins and to methods for identifying compounds interfering with an interaction of said proteins. Finally, the present invention relates to a pharmaceutical composition and to the use of compounds identified by the present invention for the preparation of a pharmaceutical composition for the treatment of Huntington's disease.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006617

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, MEDLINE, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZANZONI A ET AL: "MINT: a Molecular INTeraction database" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 513, no. 1, 20 February 2002 (2002-02-20), pages 135-140, XP004344948 ISSN: 0014-5793	1-6,8,9
Y	page 136, column 1, paragraph 2 figure 2 figure 3	7,10-12
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2004	11. 03. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helliot, B

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KLEIMAN FRIDA E ET AL: "Functional interaction of BRCA1-associated BARD1 with polyadenylation factor CstF-50" SCIENCE (WASHINGTON D C), vol. 285, no. 5433, 3 September 1999 (1999-09-03), pages 1576-1579, XP002301403 ISSN: 0036-8075 page 1576, column 2, paragraph 2 page 1576, column 2, paragraph 3 page 1576, column 2, paragraph 2 page 1577, column 1, paragraph 3 page 1578, column 3, paragraph 2 page 1579, column 1, paragraph 1 figure 1	13-24,35
X	THAI TO HOA ET AL: "Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers" HUMAN MOLECULAR GENETICS, vol. 7, no. 2, February 1998 (1998-02), pages 195-202, XP002301404 ISSN: 0964-6906 abstract	35
Y	WO 03/045990 A (HYBRIGENICS ; JACQ XAVIER (FR); LEGRAIN PIERRE (FR); COLLAND FREDERIC) 5 June 2003 (2003-06-05) page 22, lines 12-16 page 31, columns 27-31 pages 34-37; example 2 pages 56-59; example 14	7,10-12
A	US 6 235 879 B1 (GOLDBERG PAUL ET AL) 22 May 2001 (2001-05-22) column 19, paragraph 3 column 4, paragraph 3	
A	SITTLER A ET AL: "SH3GL3 ASSOCIATES WITH THE HUNTINGTIN EXON 1 PROTEIN AND PROMOTES THE FORMATION OF POLYGLN-CONTAINING PROTEIN AGGREGATES" MOLECULAR CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 2, no. 4, October 1998 (1998-10), pages 427-436, XP000973321 ISSN: 1097-2765 abstract	

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DUNAH ANTHONE W ET AL: "Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease" SCIENCE (WASHINGTON D C), vol. 296, no. 5576, 21 June 2002 (2002-06-21), pages 2238-2243, XP002304734 ISSN: 0036-8075 abstract page 2242, column 3, paragraph 3	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/006617

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: 30-31
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 30-31
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-29,32,35-36(all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 30-31

Claims 30-31 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define the subject-matter only in terms of a functional feature of the compound, namely that it has been identified by the method of claims 25-29. However, since this feature does not provide any indication as to the structure of the said compound and since claims 30-31 are silent as to the compound which is modeled, synthesized (claim 30) and further modified (claim 31), the said claims lack clarity to such an extent as to render a meaningful search impossible. Moreover, the description does not disclose any such compound either.
Thus, said claims 30-31 cannot been searched (see PCT/ISA form 206) and have not been taken into account for the assessment of non-unity. No opinion will thus be given with respect to novelty, inventive step or industrial applicability.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1 : 1-29, 32 and 35-36 (all partially).

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide, and in particular when the disease-related protein is huntingtin and more particularly when the modulator of huntingtin is BARD1.
A nucleic acid molecule encoding a modulator of huntingtin wherein said modulator is BARD1.
A vector and a host cell comprising a nucleic acid molecule encoding BARD1.
A polypeptide comprising an amino acid sequence of BARD1.
A method of producing the polypeptide comprising an amino acid sequence of BARD1.
A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second one is SETDB1.
An antibody specifically recognising BARD1.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is BARD1.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is BARD1.
A method of diagnosing Huntington's disease in a biological sample using BARD1.
A diagnostic agent/composition or pharmaceutical composition using BARD1.

1.1. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is CA150.
An antibody specifically recognizing the protein complex as set herein above.

1.2. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is NAG4.
An antibody specifically recognizing the protein complex as set herein above.

1.3. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is HIP15.
An antibody specifically recognizing the protein complex as set herein above.

1.4. claims: 22-24 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is HIP5.
An antibody specifically recognizing the protein complex as set herein above.

1.5. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is PTN.
An antibody specifically recognizing the protein complex as set herein above.

1.6. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is FEZ1.
An antibody specifically recognizing the protein complex as set herein above.

1.7. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is IKAP.
An antibody specifically recognizing the protein complex as set herein above.

1.8. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is BAIP1.
An antibody specifically recognizing the protein complex as set herein above.

1.9. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is mHAP1.
An antibody specifically recognizing the protein complex as set herein above.

1.10. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is HBO1.
An antibody specifically recognizing the protein complex as set herein above.

1.11. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is BAIP2.
An antibody specifically recognizing the protein complex as set herein above.

1.12. claims: 22-24 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is PLIP.
An antibody specifically recognizing the protein complex as set herein above.

1.13. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is PIASy.
An antibody specifically recognizing the protein complex as set herein above.

1.14. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is HZFH.
An antibody specifically recognizing the protein complex as set herein above.

1.15. claims: 22-24 (partially)

A protein complex comprising at least two proteins, wherein the first protein is BARD1 and the second is ZHX1.
An antibody specifically recognizing the protein complex as set herein above.

Inventions 2-5: 5-29 , 32, 35-36 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide, wherein the disease-related protein is huntingtin and the modulator of huntingtin is one of the modulators of Tab. 8, different from BARD1 and GIT1.
A nucleic acid molecule encoding a modulator of huntingtin wherein said modulator is one of the modulators of Tab. 8, different from BARD1 and GIT1.
A vector and a host cell comprising the nucleic acid molecule as set out herein above.
A polypeptide comprising an amino acid sequence encoding one of the modulators as set out herein above.
A method of producing the polypeptide as set out herein above.
A protein complex comprising at least two proteins, wherein the first protein is one of the other modulators as set out herein above.
An antibody specifically recognising one of the other modulators as set out herein above.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is one of the proteins of Tab. 8, different from BARD1 and GIT1.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is one of the compounds of Tab. 8, different from BARD1 and GIT1.
A method of diagnosing Huntington's disease in a biological sample using one of the compounds of Tab. 8, different from BARD1 and GIT1.
A diagnostic agent/composition or pharmaceutical composition using one of the compounds of Tab. 8, different from BARD1 and GIT1.

Invention 6: 5-29 (partially), 32 (partially), 33 (completely), 35-36 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide, wherein the disease-related protein is huntingtin and the modulator of huntingtin is GIT1.
A nucleic acid molecule encoding a modulator of huntingtin wherein said modulator is GIT1.
A vector and a host cell comprising the nucleic acid molecule as set out herein above.
A polypeptide comprising an amino acid sequence encoding GIT1.
A method of producing the polypeptide as set out herein above.
A protein complex comprising at least two proteins, wherein the first protein is GIT1.
An antibody specifically recognising GIT1 or the complex as defined herein above.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is GIT1.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is GIT1.
A method of diagnosing Huntington's disease in a biological sample using GIT.
A diagnostic agent/composition or pharmaceutical composition using GIT1.

Invention 7: 5-12 (partially), 22-29 (partially), 32 (partially), 34-36 (partially)

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide, wherein the disease-related protein is huntingtin and the modulator of huntingtin is htt as defined in Tab. 7.
A protein complex comprising at least two proteins, wherein the first protein is htt as defined in Tab. 7.
An antibody specifically recognising htt or the complex as defined herein above.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is htt.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is htt.
A method of diagnosing Huntington's disease in a biological sample using htt.
A diagnostic agent/composition or pharmaceutical composition using htt.

Invention 8: 5-12 (partially), 22-29 (partially), 32 (partially), 34-36 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide, wherein the disease-related protein is huntingtin and the modulator of huntingtin is HIP15.
A protein complex comprising at least two proteins, wherein the first protein is HIP15.
An antibody specifically recognising HIP15 or the complex as defined herein above.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is HIP15.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is HIP15.
A method of diagnosing Huntington's disease in a biological sample using HIP15.
A diagnostic agent/composition or pharmaceutical composition using HIP15.

Invention 9: 5-12 (partially), 22-29 (partially), 32 (partially), 34-36 (partially)

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide, wherein the disease-related protein is huntingtin and the modulator of huntingtin is HP28.
A protein complex comprising at least two proteins, wherein the first protein is HP28.
An antibody specifically recognising HP28 or the complex as defined herein above.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is HP28.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is HP28.
A method of diagnosing Huntington's disease in a biological sample using HP28.
A diagnostic agent/composition or pharmaceutical composition using HP28.

Inventions 10-73: 5-12 (partially), 22-29 (partially), 32 (partially), 35-36 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide,, wherein the disease-related protein is huntingtin and the modulator of huntingtin is a protein as listed in Tab. 7, insofar as the said protein does not relate to those listed in Tab. 8, to BARD1, htt, HIP15 and HP28.
Moreover, for those proteins present both in Tab. 7 and in Tab. 9, the inventions will also comprise a protein complex comprising at least two proteins, wherein the first protein is one of the protein disclosed in Tab. 9, insofar as the said protein does not relate to those listed in Tab. 8, to BARD1, htt, HIP15 and HP28.
An antibody specifically recognising the complex as defined herein above.
A method of identifying whether a protein promotes or inhibits huntingtin aggregation wherein the protein is one of the proteins selected in the Tab. 7 but different from BARD1, from those listed in Tab. 8 and from htt, HIP15 and HP28.
A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin wherein said the compound is one of the proteins selected in the Tab. 7 but different from BARD1, from those listed in Tab. 8 and from htt, HIP15 and HP28.
A method of diagnosing Huntington's disease in a biological sample using one of the proteins selected in the Tab. 7 but different from BARD1, from those listed in Tab. 8 and from htt, HIP15 and HP28.
A diagnostic agent/composition or pharmaceutical composition using one of the proteins selected in the Tab. 7 but different from BARD1, from those listed in Tab. 8 and from htt, HIP15 and HP28.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/006617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03045990 A	05-06-2003	AU 2002365517 A1	10-06-2003
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US 6235879 B1	22-05-2001	AU 4212199 A	13-12-1999
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